Impact of Peripheral Vascular Disease on Short- and Long-term Outcomes in Patients Undergoing Non-Emergent Percutaneous Coronary Intervention in the Drug-Eluting Stent Era

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ABSTRACT: Objectives. This study sought to compare short- and long-term (4-year) outcomes in patients with and without peripheral vascular disease (PVD) following non-emergent percutaneous coronary intervention (PCI) in current clinical practice. **Background.** Patients with PVD undergoing coronary revascularization have high rates of adverse short-term outcomes. However, the long-term clinical outcomes of patients with PVD undergoing PCI in the contemporary drug-eluting stent (DES) era have not been well characterized. **Methods.** The 2004/2005 Cornell Angioplasty Registry database was used to evaluate the in-hospital and long-term clinical outcomes in patients undergoing non-emergent (urgent or elective) PCI. A total of 2455 study patients were examined. We excluded patients presenting with an ST-elevation myocardial infarction (MI) ≤24 hours, hemodynamic instability/shock, thrombolytic therapy ≤7 days, or renal insufficiency (creatinine ≥4 mg/dL). Mean clinical follow-up was 4.4 ± 1.1 years. **Results.** Of the 2455 patients, a total of 173 (7%) had PVD and 2282 (93%) had no reported history of PVD. DESs were used in 87% of the PCIs. The incidence of in-hospital death (1.8% vs 0.1%; *P*=.006) was greater in the PVD group, whereas postprocedural MI (6.4% vs 6.8%; *P*=.810) and major adverse cardiovascular event rates including death, stroke, emergent coronary artery bypass graft/PCI, and MI (8.7% vs 7.0%; *P*=.360) were similar in the PVD versus no PVD groups. Long-term Kaplan-Meier survival (89.2% vs 76.2%; *P*<.001) was significantly higher in patients without PVD versus with PVD, respectively. After adjustment with a multivariate Cox regression analysis, long-term all-cause survival was similar in patients with versus without PVD (hazard ratio, 1.16; 95% confidence interval, 0.69-1.93; *P*=.581). **Conclusions.** In contemporary PCI utilizing DESs, glycoprotein IIb/IIIa inhibitors, and clopidogrel, PVD is associated with a higher in-hospital and 4-year all-cause mortality. In our study, this difference in long-term survival was mainly driven by a higher rate of comorbidities in the PVD population that underwent PCI.

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Peripheral vascular disease (PVD) frequently coexists with coronary artery disease (CAD) in patients undergoing percutaneous coronary intervention (PCI). Approximately one-third of elderly patients with coronary disease have concomitant PVD, whereas two-thirds of PVD patients have coronary disease.[1,2] Patients with PVD have significantly higher mortality rates that are approximately 7 times higher than individuals without PVD when followed prospectively for up to 10 years.[3] PVD also portends worse short-term outcomes in patients undergoing coronary revascularization via surgical bypass grafting[4,5] or PCI with bare-metal stent (BMS) implantation.[6] In the BMS era, PVD has been shown to be an independent predictor of in-hospital mortality and adverse events post PCI.[6] Two-year follow-up of patients with versus without PVD undergoing PCI with BMS demonstrated a decreased survival in those with PVD.[6]

The etiology of increased mortality in PVD patients undergoing coronary revascularization is thought to be linked to other cardiovascular morbidities and is commonly secondary to congestive heart failure and fatal dysrhythmias rather than cerebrovascular accidents or peripheral arterial complications. In the OPUS-TIMI 16 study,[7] PVD patients with acute coronary syndromes appeared to receive less aggressive medical therapy relative to their burden of coronary atherosclerosis, which may also explain their worse outcomes. However, to date, there are limited outcomes data in PVD patients undergoing PCI in the drug-eluting stent (DES) era, where application of more aggressive antiplatelet therapies exists. The objective of this study was to compare the in-hospital and long-term (4-year) outcomes in patients with versus without PVD after undergoing PCI in contemporary interventional practice utilizing DESs.

Methods

Data collection. The Cornell Angioplasty Registry includes all patients undergoing PCI at our institution. A standard case report form delineating comprehensive patient demographics, preintervention clinical status, procedural findings, and in-hospital complications was completed for each PCI performed. Patients undergoing PCI between January 1, 2004 and December 31, 2005 who met inclusion criteria were enrolled in this study. Patient follow-up was obtained by means of publicly available mortality data through the Social Security Death Index[8] as well as through regularly scheduled phone contact. Baseline CK, CK-MB, and troponin I levels were obtained routinely prior to PCI and 8, 12,

and 18 hours after PCI. Only the initial PCI was included in this analysis for patients undergoing multiple PCIs during the defined study period. The study was approved by the institutional review board of the Weill Medical College of Cornell University.

Procedural data. Bivalirudin was administered as a 0.75 mg/kg intravenous (IV) bolus followed by an infusion of 1.75 mg/kg/hour for the duration of the PCI procedure. Abciximab was administered as a 0.25 mg/kg bolus and a 0.125 µg/kg/minute (maximum, 10 µg/minute) infusion for 12 hours. Eptifibatide was given as two 180 µg/kg boluses 10 minutes apart, followed by a 2.0 µg/kg/minute infusion for 18 hours. Aspirin (325 mg) was routinely administered prior to PCI. Clopidogrel (300 mg or 600 mg loading dose) was administered before or immediately after the PCI, followed by 75 mg/day for at least 3-12 months. The administration of IV glycoprotein (GP) IIb/IIIa inhibitors, the choice of BMS or DES, and the timing of thienopyridine pretreatment were at the discretion of the physician.

Data analysis. Patients presenting with an acute ST-elevation MI (STEMI) ≤24 hours, hemodynamic instability/shock, use of thrombolytic therapy ≤7 days, or with renal insufficiency (serum creatinine ≥4 mg/dL) were excluded. Baseline patient clinical characteristics and angiographic data were compared between patients with and without PVD. The primary endpoints analyzed were in-hospital mortality after PCI and long-term all-cause mortality. The secondary endpoints included the incidence of in-hospital major adverse cardiovascular events (MACE), MI, major and minor bleeding. Long-term mortality data were obtained for 98% of patients, with a mean follow-up of 4.4 ± 1.1 years.

Definitions. *Peripheral vascular disease* was defined as carotid, aorto-femoral, or lower-extremity vascular disease documented by a radiological study, history of vascular intervention or of a cerebral vascular accident. *MI before PCI* was defined as any elevation of CK-MB or troponin I level greater than the laboratory upper limits of normal (ULN). *MI after PCI* was defined as CK-MB ≥3 times the ULN within 24 hours post PCI and at least 50% increase over the preprocedural levels. *Multivessel disease* was defined as the presence of >70% lesion in ≥2 major coronary arteries/branches or a left main coronary artery lesion of >50%. *Multivessel PCI* was defined as a coronary intervention in ≥2 major coronary arteries/branches or in the left main coronary artery. *Multilesion PCI* was defined as a coronary intervention in ≥2 lesions of a single coronary artery or multiple coronary arteries. *Congestive heart failure (CHF)* referred to patients having New York Heart Association Class III or IV heart failure during admission. *MACE* was defined as post-PCI death, emergency cardiac surgery, emergency PCI, cerebral vascular accident, or MI. *Vascular injury* referred to an access-site complication requiring mechanical intervention. *Major bleeding* was defined as a drop in hemoglobin ≥4 g/dL. *Minor bleeding* was defined as a drop in hemoglobin ≥2 g/dL and <4 g/dL. *Angiographic success* was defined as a final stenosis of ≤20% of the vessel diameter with the use of any PCI.

Statistical analysis. Data management and analysis were performed using SPSS version 18.0 (SPSS, Inc). Data are presented as the mean value ± standard deviation for continuous variables or as proportions for dichotomous variables. Differences in baseline characteristics and comorbid conditions between groups were compared with the chi-square (χ^2) test or the Fisher exact test for dichotomous variables, and mean values for continuous variables were compared with the Student's t-test. Stepwise multivariate logistic regression was performed to determine the independent effect of PVD on occurrence of in-hospital events. Long-term mortality rates were calculated and plotted according to the Kaplan Meier methods, and comparisons between the two treatment groups were performed using the log rank statistic. The relation of PVD to the risk of long-term mortality was assessed with Cox proportional hazards models. Univariate associations were estimated for all clinical and procedural variables (Tables 1 and 2). To test the independence of PVD as a predictor of long-term mortality, PVD variable was entered into a multivariable Cox proportional hazards model that also included univariate predictors of long-term mortality (significant at the level of .15). For all tests, a two-tailed value of $P<.05$ was required for statistical significance.

Results

Patient population. Between January 1, 2004 and December 31, 2005, a total of 2455 patients meeting study criteria underwent urgent or elective PCI. One hundred seventy-three patients (7%) had PVD and 2282 patients (93%) had no reported history of PVD. The baseline clinical characteristics and angiographic data are listed in Table 1. The majority of patients in both groups were older Caucasian men presenting with unstable angina. The PVD group had a significantly greater prevalence of diabetes, CHF, prior cerebrovascular accident (CVA), prior coronary artery bypass graft (CABG), and chronic renal insufficiency. Patients with PVD were more likely to present with multivessel or left main disease and to undergo an urgent intervention as compared with patients without PVD. DESs were used in 87% of PCIs. DESs and GP IIb/IIIa inhibitors were used less frequently in patients with PVD.

In-hospital outcomes. Angiographic success was similarly high in both groups (Table 2). The overall mortality for the entire study sample was low (0.20%). The unadjusted incidence of in-hospital mortality (1.8% vs 0.1%; odds ratio [OR], 13.41; 95% confidence interval [CI], 2.69-66.93; P=.006) was greater in the PVD cohort, whereas postprocedural MI (6.4% vs 6.8%; OR, 0.93; 95% CI, 0.49-1.74; P=.810) and MACE rates (8.7% vs 7.0%; OR, 1.36; 95% CI, 0.81-2.30; P=.360) were comparable between the two groups. The incidence of major bleeding events was greater in the PVD group (2.9% vs 1.1%; OR, 2.58; 95% CI, 1.00-6.81; P=.049). After adjustment for baseline differences with multivariate logistic modeling, presence of PVD was no longer predictive of in-hospital mortality (OR, 3.69; 95% CI, 0.52-26.40; P=.194) as well as MI (OR, 0.76; 95% CI, 0.39-1.49; P=.423) or MACE (OR, 1.33; 95% CI, 0.82-2.16; P=.251).

Long-term outcomes. At 1 year, there were 14 deaths (8.2%) in the PVD group versus 66 (2.9%) in the non-PVD group (HR, 2.82; χ^2=13.35; 95% CI, 1.62-4.92; P=.001). At follow-up (mean, 4.4 ± 1.1 years), all-cause mortality was significantly higher in the PVD group, 41 deaths (23.8%) versus 246 (10.8%) in the non-PVD group (P log-rank <.001)

Table 1. Demographic and clinical characteristics.

	PVD (n = 173)	No PVD (n = 2282)	*P*-Value
Age (years)	70.4 ± 11.0	66.6 ± 11.8	<.001
Men	72.8%	69.1%	.347
Caucasian	79.8%	78.8%	.847
Diabetes mellitus	39.9%	30.8%	<.001
Body mass index (kg/m^2)	28.5 ± 5.8	28.6 ± 5.3	.841
Current CHF	17.9%	8.5%	<.001
LVEF (%)	48.0 ± 11.5	50.5 ± 10.0	.002
Unstable angina/NSTEMI	58.4%	56.9%	.689
COPD	6.4%	4.8%	.361
Prior stroke	18.5%	7.4%	<.001
Prior CHF	5.8%	2.1%	.007
Prior myocardial infarction	45.7%	40.5%	.199
Prior PCI	28.7%	32.4%	.339
Prior CABG	27.2%	15.2%	<.001
Hemoglobin level (g/dL)	12.3 ± 1.8	13.1 ± 1.7	<.001
Creatinine clearance (mL/min)	66.0 ± 37.0	77.9 ± 32.9	<.001
Urgent procedure	61.2%	51.4%	.017
Number of diseased coronary arteries			
One	31.2%	38.8%	.05
Two	42.4%	36.2%	.117
Three	18.2%	17.2%	.752
Multivessel or left main disease	62.4%	54.2%	.045
Target coronary artery in PCI			
LAD	35.3%	49.9%	<.001
Right coronary artery	41.2%	30.2%	.003
Left circumflex	30.6%	29.8%	.862
Left main	2.9%	1.8%	.243
Saphenous vein graft	8.8%	4.2%	.011
Multivessel or left main PCI	15.9%	15.0%	.739
Multilesion PCI	42.9%	48.1%	.203
Stent	92.4%	94.4%	.301
Drug-eluting stent	73.5%	87.8%	<.001
Glycoprotein IIb/IIIa inhibitors used	41.8%	52.5%	.008
Abciximab	5.3%	8.0%	.237
Eptifibatide or tirofiban	36.5%	44.5%	.045
Stenosis severity before PCI (%)	84.3 ± 9.4	83.9 ± 11.3	.658
Stenosis severity after PCI (%)	3.4 ± 10.0	3.0 ± 10.4	.630

Data given as mean ± standard deviation or percentage.
CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; LAD = left anterior descending coronary artery.

(Figure 1). In a univariate Cox analysis, PVD was associated with an increased risk of long-term mortality (HR, 2.34; χ^2=11.75; 95% CI, 1.44-3.81; *P*=.001) (Table 3). The independent relation of PVD and long-term mortality was examined by using a multivariate logistic regression model. After adjustment for confounding variables with multivariate Cox analysis, PVD was no longer an independent predictor of 1-year mortality (HR, 1.59; χ^2=2.43; 95% CI, 0.89-2.84; *P*=.119) or long-term mortality (HR, 1.16; χ^2=0.03; 95% CI, 0.69-1.93; *P*=.581). Table 4 lists other independent predictors of long-term all-cause mortality identified in the multivariate Cox model.

Discussion

This study represents a contemporary evaluation of PVD patients undergoing PCI and their short- and long-term outcomes in a high-volume metropolitan center. A broad spectrum of patients undergoing urgent (mild-to-moderate risk acute coronary syndrome) or elective PCI was evaluated. Patients with PVD fared worse with regard to in-hospital, 1-year, and long-term mortality, largely driven by a higher rate of comorbidities in the PVD population.

Prior studies have consistently shown that patients with PVD experience higher mortality after coronary interventions. Our analysis is unique in that we evaluated outcomes of PVD patients undergoing DES PCI in a contemporary setting where more advanced stent technology and aggressive adjunctive anticoagulant and antiplatelet therapy were utilized. Despite this, our analysis still demonstrates increased unadjusted mortality and worse clinical outcomes in the PVD group. There are several hypotheses as to why PVD patients have worse clinical outcomes compared with patients without PVD. PVD patients may have more advanced and diffuse systemic atherosclerotic burden and heightened procoagulant and proinflammatory states. Some investigators have proposed that PVD patients are less likely to be offered and to be compliant with evidence-based medical therapy including statins and beta-blockers.[9] Others have argued that PVD patients are less likely to participate

Table 2. In-hospital clinical outcomes.

	PVD (n = 173)	No PVD (n = 2282)	*P*-Value
Angiographic success	98.8%	99.6%	.153
Death	1.8%	0.1%	.006
Emergency revascularization	0.0%	0.2%	1.000
Stroke	0.6%	0.1%	.197
Renal failure	0.6%	0.1%	.254
Access-site injury	0.6%	0.0%	1.000
Stent thrombosis	0.0%	0.3%	1.000
Any bleeding	16.5%	13.0%	.197
Major bleeding	2.9%	1.1%	.049
Minor bleeding	13.5%	11.9%	.540
Myocardial infarction	6.4%	6.8%	.810
Major adverse cardiac events	8.7%	7.0%	.360

Table 3. Univariate predictors of long-term all-cause mortality (univariable Cox regression analysis).

	χ^2	95% CI	Hazard Ratio	*P*-Value
Current congestive heart failure	45.99	2.62-5.74	3.88	<.001
Prior congestive heart failure	15.68	1.93-7.02	3.68	<.001
Chronic obstructive pulmonary disease	16.38	1.75-4.98	2.95	<.001
Prior stroke	16.39	1.62-3.98	2.54	<.001
Peripheral vascular disease	11.75	1.44-3.81	2.34	<.001
Urgent procedure	10.42	1.27-2.65	1.83	.001
Diabetes mellitus	9.827	1.23-2.47	1.74	.002
Prior coronary bypass surgery	5.88	1.10-2.47	1.65	.015
Age (per year)	56.90	1.05-1.09	1.07	<.001
Creatinine clearance (per mL/min)	60.38	0.96-0.98	0.97	<.001
Left ventricular ejection fraction (per %)	26.21	0.95-0.98	0.96	<.001
Body mass index (per kg/m^2)	7.068	0.92-0.99	0.95	.008
Hemoglobin level (per g/dL)	53.50	0.63-0.77	0.70	<.001
Glycoprotein IIb/IIIa agent use	15.70	0.34-0.69	0.48	<.001
Drug-eluting stent use	38.84	0.21-0.45	0.31	<.001

and benefit from a cardiac rehabilitation program, perhaps due to poor functional status, which may contribute to their poor long-term survival.[10]

The PVD group from our registry had greater unadjusted in-hospital, 1-year, and long-term mortality rates compared with the non-PVD group. Our in-hospital mortality rate of 1.8% in the PVD group is consistent with other registry data.[11] In the NHLBI Dynamic registry, there was a 2% incidence of in-hospital mortality in the DES arm of the PVD patients.[11] The incidence of MACE in our study was lower than the NHLBI registry. Berger et al reviewed a similar large cohort of patients from the New York State Coronary Angioplasty Registry and demonstrated a significant relationship between vascular disease burden and in-hospital mortality.[12] They reported a 0.7% in-hospital mortality in patients with CAD alone following PCI with primarily bare-metal stenting. The in-hospital mortality increased to 2.6% in patients with CAD and concomitant vascular disease in 2 or more additional beds (*P*<.001). After multivariate adjustment, the extent of vascular disease remained an independent predictor of in-hospital mortality. They also reported that patients with more extensive vascular disease in addition to CAD had a greater incidence of left main/multivessel CAD as well as cardiogenic shock.[12]

Nikolsky et al found PAD to be an independent predictor of 1-year mortality, but not of adjusted in-hospital mortality.[13] In contrast to our study, their patient population had a larger proportion of PVD patients (18.9%) and therefore, the analysis may have been better powered to detect a true mortality difference. However, the Nikolsky study did not utilize DESs for PCI and only half of the patients received BMSs. This resulted in less aggressive medical therapy as clopidogrel was prescribed for a shorter duration than in our more contemporary study. Perhaps more aggressive medical therapy combined with technological improvements in PCI (eg, DES use) has resulted in improved outcomes in the PVD population examined in our study.

After a thorough multivariate analysis, we found that long-term survival was similar between PVD and non-PVD patients. The difference in long-term survival was mainly driven by a higher rate of comorbidities in the PVD population that underwent PCI. Therefore, PVD may act as a marker of poor prognosis in this high-risk group of patients with severe, diffuse atherosclerosis in multiple vascular beds, and in patients with presence of multiple risk factors that negatively impact long-term survival (eg, CHF, COPD, diabetes mellitus). Guerrero et al reported outcomes from the PAMI trials by examining a subgroup of patients with PVD and the effects of PVD in the setting of acute MI. Similar to our study, they demonstrated that patients with PVD were older and had more comorbidities including CHF, multivessel disease, and history of coronary revascularization. PVD patients had a two-fold increase in in-hospital mortality (5.3% vs 2.6%; *P*<.0001) that remained significant at 1-year follow-up (12.6% vs 6%; *P*<.0001).[14] In their analysis, the presence of PVD was an independent predictor of in-hospital mortality and death at 1 year.[14] It should be noted that their study included patients presenting with ST-elevation MI or new left bundle branch block and, therefore, represented a higher-risk ACS population. Stents were only used in 36%

Table 4. Independent predictors of long-term all-cause mortality (multivariable Cox regression analysis).

	χ^2	95% CI	Hazard Ratio	P-Value
Peripheral vascular disease	0.31	0.69-1.93	1.16	.581
Chronic obstructive pulmonary disease	12.29	1.53-4.49	2.62	<.001
Current congestive heart failure	3.78	1.00-2.67	1.63	.052
Diabetes mellitus	5.69	1.09-2.30	1.61	.017
Age (per year)	7.17	1.01-1.06	1.03	.007
Left ventricular ejection fraction (per %)	7.11	0.96-0.99	0.98	.008
Hemoglobin level (per g/dL)	9.44	0.75-0.94	0.84	.002
Drug-eluting stent use	14.23	0.19-0.59	0.33	<.001

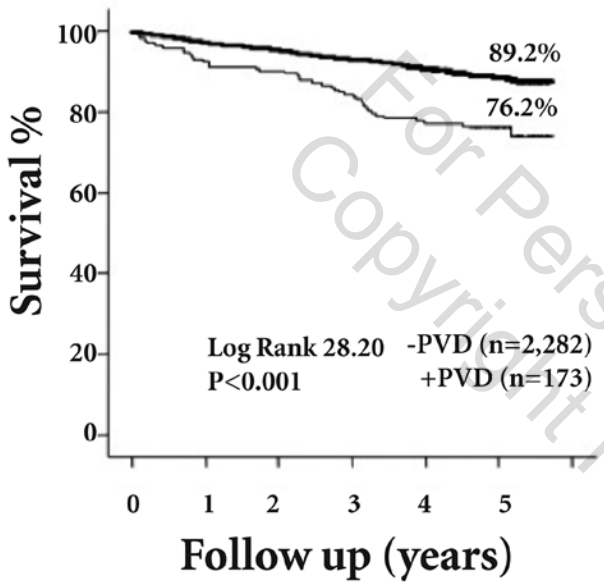

Figure 1. *Kaplan-Meier curves comparing all-cause mortality rates at follow-up between patients with and without PVD following PCI.*

of their PVD group. Furthermore, their PVD patients were less likely to undergo angioplasty and to receive beta-blocker therapy. It is possible that their PVD cohort was a higher-risk group, with more extensive coronary disease, not amenable to angioplasty. Given that PVD may be an important marker of severity of atherosclerosis and multiple comorbidities that negatively impact long-term survival, patients with PVD may benefit from more intensive outpatient monitoring/treatment of CAD risk factors after undergoing coronary stenting in contemporary clinical practice.

Study limitations. There are several limitations to this study. First, our analysis was derived from a single high-volume tertiary-care center population and thus might not apply to other institutions. Second, although data in the present study were collected prospectively, this is a retrospective analysis and is subject to the limitations of such analyses. Treatment decisions regarding access site, choice of antithrombotic therapy, and technical aspects of PCI were made by the individual physician and might have been influenced by the procedure, operator, and other factors that could not be identified by our registry. Third, our analysis had a relatively small number of patients with PVD and, therefore, may have been underpowered to detect a true difference in mortality. Finally, we included patients with symptomatic or radiologically documented PVD, which preselected for a higher-risk PVD population undergoing PCI. Patients with asymptomatic PVD were not included in our PVD group.

Conclusions

In contemporary PCI utilizing DESs, GP IIb/IIIa inhibitors, and clopidogrel, PVD is associated with a higher in-hospital and 4-year all-cause mortality. In our study, this difference in long-term survival was mainly driven by a higher rate of comorbidities in the PVD population that underwent PCI. PVD may be an important marker of severity of atherosclerosis and multiple comorbidities that negatively impact long-term survival. Therefore, patients with PVD may benefit from more intensive outpatient monitoring and treatment of CAD and risk factors after undergoing coronary stenting.

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